Catastrophic Antiphospholipid Syndrome; A "CATASTROPHIC" Case of Systemic Lupus Erythematosus

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Abstract

Less than 1% of patients with the antiphospholipid antibody syndrome (APS) can develop multiple, simultaneous organ-system thromboembolic disease, which is referred to as the catastrophic antiphospholipid antibody syndrome (CAPS). Roughly one-half of these patients have systemic lupus erythematosus (SLE). Factors known to precipitate CAPS include infection, surgery, trauma, neoplasia, anticoagulation withdrawal, obstetric complications, and SLE flares. Optimal treatment includes anticoagulation and high-dose corticosteroids, although IVIG and plasma exchange may also have a role. The overall mortality of CAPS is roughly 50%, but prompt clinical recognition of this rare but devastating syndrome may lead to improved outcomes.

Catastrophic antiphospholipid antibody syndrome (CAPS) is a rare clinical subset of the antiphospholipid antibody syndrome (APS), occurring in less than 1% of patients. This syndrome presents acutely with multi-organ thrombosis and failure, with an associated 50% mortality rate. We describe an illustrative case and discuss risk factors, clinical features and treatment options for this uncommon yet devastating syndrome.

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Case Report

A 37 year-old Caucasian female presented to our facility with a diagnosis of systemic lupus erythematosus (SLE). Her disease was manifested previously by arthritis, pleurisy, Raynaud's phenomenon, hypocomplementemia, positive autoantibodies (antinuclear, double-stranded DNA, and ribonucleoprotein) and a positive lupus anticoagulant test without prior thrombotic events. Her disease was stable on hydroxychloroquine and low-dose prednisone. Several months later, she presented to her primary care clinic with symptoms of dysuria and a urinalysis that revealed pyuria with bacteruria. She was treated with sulfamethoxazole/trimethoprim, but presented at our institution three days later complaining of nausea, vomiting, low-grade fever and diffuse abdominal discomfort.

Physical examination revealed mild tachycardia, fever to 101.0 F, and diffuse abdominal tenderness without organomegaly or peritoneal signs. She was neurologically intact and her skin exam did not reveal cyanosis, livedo reticularis, petechiae or purpura. Laboratory studies revealed a normal white blood cell count of 5,900 per mm^3 (3.5-11.0), low hemoglobin 5.7 g/dL (11.7-15.7) and hematocrit 15% (35.1-47.1), elevated mean corpuscular volume 112 fL (80-100), and low platelet count of 113,000 (150,000-440,000). The peripheral smear showed polychromasia, mild thrombocytopenia without clumping, and no schistocytes. Her serum creatinine, electrolytes, and hepatic panel were normal but coagulation studies revealed mild prolongation of prothrombin and partial thromboplastin times at 13 seconds (10.7-13.1) and 46 seconds (24-38), respectively. Fibrinogen was normal but haptoglobin was < 20 mg/dl (30-200), lactate dehydrogenase was elevated at 885 U/L (94-250), Coomb's direct antibody test was positive and the reticulocyte count was elevated at 16.7% (0.5-1.5). Urinalysis was unremarkable except for trace protein.

She was felt to have profound hemolytic anemia, which was treated with high-dose intravenous corticosteroids (1,000 mg of methylprednisolone twice per day) and intravenous gammaglobulin (IVIG) (1 gram per kilogram). She was transfused with only one unit of packed red blood cells because she had cross-reacting antibodies to all other available units in our blood bank. Her hematocrit stabilized at 26% and her platelet count improved to 246,000. The PTT remained prolonged and did not correct with 1:1 mixing studies, lupus anticoagulant (by diluted Russell viper venom time) was positive and fibrin D-dimer was elevated at 2.2 ug/mL (< 0.5). Computerized tomography of the chest and abdomen revealed multiple bilateral lung alveolar opacities, small bilateral pleural effusions, pericholecystic fluid and hypodensities in the spleen and kidneys consistent with infarctions.

Her condition rapidly deteriorated, manifested by increased respiratory distress and hypoxemia, which ultimately required mechanical ventilation, along with mental status changes. Pulmonary artery catheterization showed elevated pulmonary arterial pressures with

a normal pulmonary capillary wedge pressure. Given her elevated D-dimer, hypercoagulability (positive lupus anticoagulant) and elevated pulmonary artery pressures, a diagnosis of pulmonary embolus was considered and thrombolytic therapy entertained. However, fibrinolytic therapy was felt to be relatively contraindicated given her acute mental status changes, profound anemia and mild thrombocytopenia without available blood product support in case of a hemorrhage. A head CT was quickly done to assess for intracranial hemorrhage and a CT pulmonary angiogram performed to evaluate for pulmonary embolus, but both studies were unremarkable.

Her pulmonary artery catheterization, chest radiograph and clinical findings were felt to be consistent with adult respiratory distress syndrome (ARDS), but she eventually expired despite aggressive management. An autopsy revealed splenic and renal infarctions with thrombosis, pericardial and pleural effusions, and pulmonary edema. Several small and medium-sized vessels in both lungs had thrombi and a large thrombus was observed in her right ventricle. Her clinical findings of hemolytic anemia, multi-organ thrombosis, and ARDS in association with positive lupus anticoagulant were consistent with a post-mortem diagnosis of CAPS.

Discussion

CAPS was only recently described as a rare manifestation of APS associated with multiple vascular occlusive events and multi-organ failure, with the first reported case in 1992 by Asherson.[1] He later provided a comprehensive and detailed review of the clinical and laboratory features of CAPS in 1998,[2] but expanded this review three years later to include a total of 80 patients collected from multiple medical centers.[3]

There is no general concensus regarding the diagnostic criteria for the diagnosis of CAPS, but most accept the presence of thrombotic vascular occlusion in at least three different organ systems, presenting acutely over days to weeks, in patients with antiphospholipid antibodies.[4] A recent international workshop on APS discussed diagnostic criteria for the classification of CAPS. They proposed four criteria, to include involvement of at least three organ systems and/or tissues, onset in less than one week, histopathologic confirmation of small vessel involvement in at least one organ or tissue, and laboratory confirmation of antiphospholipid antibodies. A definite diagnosis of CAPS was considered when all four criteria were met, while a probable diagnosis was considered when only two organs and/or tissues were involved (Table 1).[5,6]

Thrombosis appears to occur equally in arteries and veins in CAPS, but females are affected three times more often than men, with the mean age of onset being 37 years.[3] In a review of 1,000 patients with APS over a seven-year period, the incidence of CAPS was noted to be 0.8%. Interestingly, CAPS was the presenting manifestation in 6 of the 8 patients who ultimately developed this. Roughly one-half of those affected with CAPS also had systemic lupus erythematosus (SLE) while the other half appeared to have primary APS (Table 2).[7]

The pathogenesis of CAPS is unknown, but precipitating factors have been identified such as preceding infections (35%), surgery or trauma (13%), neoplasia (8%), anticoagulation withdrawal (8%), obstetric complications (6%), SLE flares (5%), and oral contraceptive use (35%). No precipitating factor is identified in approximately one-third of patients.[3] Kitchens discussed a "thrombotic storm" theory,[8] where thrombosis leads to additional thrombosis and fibrinolytic shutdown. Others have proposed a "double/triple" hit theory, where a patient with SLE or malignancy has an infection, trauma, or surgery and anticoagulation is withheld, leading to a cascade of thrombotic complications.[9]

There are several common clinical and laboratory manifestations of CAPS (Table 2). The most common clinical findings include cardiopulmonary involvement (25%) (pulmonary embolus and ARDS), CNS involvement (22%), abdominal pain (22%), and fever (10%). These were all clinical manifestations noted in our patient. Less common presenting manifestations include renal impairment (14%) and cutaneous involvement (9%). Any organ system may ultimately be affected, but organs most commonly affected were kidneys (78%), lungs (66%), CNS (56%), heart (50%), skin (50%), and hematologic (with diffuse intravascular coagulation) (25%). Common laboratory findings include thrombocytopenia (60%), hemolytic anemia (39%), features of DIC (19%), and schistocytes on peripheral smear (9%). As mentioned previously, all

Table 1.— Recently adapted diagnostic criteria for the classification of CAPS.[5]

Diagnostic criteria used in the classification of CAPS
1) Involvement of at least three or more organ systems and/or tissues
2) Onset in less than one week
3) Histopathologic confirmation of small vessel involvement in at least one organ or tissue
4) Laboratory confirmation of antiphospholipid antibodies
Definite diagnosis considered when all four criteria are met.
Probable diagnosis considered when only two organs and/or tissues are involved.

patients with CAPS have antiphospholipid antibodies, with 86% having high-titer cardiolipin antibodies and 68% having lupus anticoagulant.[3]

Many treatments have been used in CAPS, with varying degrees of success (Table 3). Therapy with anticoagulation (84%) and steroids (80%) was seen most commonly in Asherson's review, but other treatments include plasmapheresis (20%) and IVIG (19%). Despite aggressive treatment, the mortality rate of CAPS approaches 50%, with death typically secondary to ARDS and/or multi-organ failure. No therapeutic interventions have clearly been shown to improve survival to date,[3] although these patients should be managed in an intensive care setting and strong consideration should be given to the use of anticoagulation and high-doses of steroids. Possible precipitating factors should be treated and or eliminated. Antibiotics for suspected infections should be given and debridement of necrotic tissue should be performed. Second line treatment options include IVIG and/or plasma exchange with or without fresh frozen plasma. Cyclophosphamide should be considered in patients not responding to therapy, especially in the setting of an SLE flare.[5,6] Our patient received high-dose corticosteroids and IVIG, but did not receive anticoagulation, plasmapheresis or cyclophosphamide.

Our patient presented with severe hemolytic anemia and rapidly developed multi-organ failure with ARDS. Her case appears to be representative of the typical clinical manifestations and outcome seen with CAPS. Fortunately, this syndrome only occurs in less than 1% of all patients with APS but usually presents acutely. The diagnosis is usually made by clinical, laboratory, radiologic and histopathologic findings but ante-mortem diagnosis can be elusive. Increased physician awareness of this syndrome hopefully will result in more rapid diagnosis and treatment, though it remains to be determined if this will ultimately lead to improved clinical outcomes.

Table 2.— Common clinical and laboratory findings in CAPS.

Clinical	Laboratory
Cardiopulmonary (pulmonary embolus and ARDS)	Anticardiolipin antibodies
CNS involvement (stroke and mental status changes)	Lupus anticoagulant
Abdominal pain	Thrombocytopenia
Fever	Hemolytic anemia
Renal impairment	Features of DIC
Cutaneous involvement	Schistocytes

Table 3.— Therapeutic modalities used in the treatment of CAPS.

Anticoagulation
Corticosteroids
Antibiotics for suspected infections
Debridement of any necrotic tissue
Consider IVIG and/or plasma exchange as second line therapy
Consider cyclophosphamide if not responding to the above therapies

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